REMARKS

Entry of the foregoing and favorable reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R.§ 1.112, and in light of the remarks which follow are respectfully requested.

By the present amendment the specification has been amended to update the continuity data to include PCT/FR93/000264, filed March 16, 1993, WO9319191. Claims 19 to 22 have been deleted without prejudice or disclaimer of the subject matter contained therein. These claims were deleted solely to expedite the prosecution of the present application and not to acquiesce to the Examiners rejections. Applicants reserve their rights to file a continued prosecution application or an RCE directed towards the canceled subject matter.

Claims 15 to 18 have been amended for further clarification. Claims 23 to 25 has been added. Support for new Claim 23 can be found at least on page 14, line 9 of the specification as filed. Support for new Claim 24 can be found at least on page 4, lines 9 to 10 and at least page 13, lines 11 to 20, with respect to the injection. Support for new Claim 25, can be found at least on page 13, lines 5-10 and at least on page 6, lines 6 to 7. Applicants submit that no new matter has been added via this amendment.

Priority

Turning now to the Official Action, the Examiner has requested that Applicants include application PCT/FR93/00264, filed 3-16-93, WO9319191 in the status of the application such that there is no gap in the chain of priority. Applicants have amended the specification accordingly, which renders this objection now moot.

Claim Objections

The Examiner has objected to the claims for containing various terminology. Claims 19-22 have been cancelled rendering the objection of these claims moot. As far as these objections may pertain to the newly amended claims of record, Applicants submit that the terminology "an insert containing," "wherein the insert is," "those sequences which carry genetic information," a set of," "the transactivators", "genomic sequence of the" and "placed" have been deleted from the claims. Therefore, these objections should be rendered moot.

35 U.S.C. §112

1) Claims 15 to 22 have been rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art, at the time the application was filed, that the inventors had possession of the claimed invention. This rejection has been obviated-in-part by amendment and is being traversed in part.

Claims 19 to 22 have been cancelled and therefore, the rejections pertaining to these claims have been rendered moot.

With respect to the rejection of claims 15 to 19, Applicants offer the following remarks.

The Examiner purports that the limitation of "a pharmaceutical composition comprising an adenovirus" and a "pharmaceutically acceptable vehicle" (claim 15) does not have support in the specification as originally filed. The Examiners attention is drawn to at least the paragraph bridging pages 6 and 7 of the application as filed. More specifically this paragraph states the

following:

> "The invention also relates to pharmaceutical compositions comprising one or more recombinant vectors as described above, in combination with a pharmaceutically acceptable vehicle, especially sterile, isotonic compositions which can be injected directly into the tumors to be treated, or dry, in particularly ophilized, compositions which, by the addition of sterilized water or of physiological saline as the case may be, enable solutions which can be injected directly into the tumors to be made up or reconstituted."

Therefore, Applicants submit that "a pharmaceutical composition" is in fact described in the specification and would convey to the skilled artisan that Applicants had possession at the pharmaceutical composition at the time that this application was filed.

The Examiner purports that the terms "endogenous" or "heterologous" promoters does not have support in the specification as originally filed. The Examiner's attention is drawn to at least page 2, lines 20 to 23 of the present application which mentions that the nucleic acid sequence coding for a cytokine is under the control of a promoter present in the adenovirus genomic sequence (endogenous promoter) or of a promoter inserted in the adenovirus genomic sequence (heterologous promoter). In addition the specification illustrates endogenous promoters such as MLP (page 10, line 2 and page 14, line 26) and E1A promoters (page 14, line 19), as well as a series of heterologous promoters (page 14, lines 4 to 14), such as the LTR of RSV, the IE gene of CMV, the MMTV promoter and the like.

Therefore, Applicants submit that there is support in the specification as filed for endogenous and heterologous promoters.

As far as new Claim 24 is concerned, support can be found at least on page 4, lines 9 to 10 and at least page 13, lines 11 to 20, with respect to the injection. Support for new Claim 25, can be found at least on page 5, lines 24 to page 6, lines 6 to 7. Therefore, Applicants submit that the newly added claims are supported by the application as filed.

In view of the above, withdrawal of this rejection is respectfully requested.

2) Claims 15 to 22 have been rejected under 35 U.S.C. § 112, first paragraph as lacking written description. In rendering this rejection, the Examiner purports that the specification does not sufficiently describe "replication defective adenoviruses encoding a cytokine gene operatively linked to an early or heterologous promoter to treat a tumor in a patient." For the following reasons, this rejection is respectfully traversed.

The Examiner has failed to consider that there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. According to the Guidelines for examination of patent applications under 35 U.S.C.§ 112, first paragraph for the written description requirement (January 5, 2001), the burden is on the Examiner to establish a *prima facie* case of failure to comply with the written description requirement. This can be established by **providing reasons why a person skilled in the at the time of filing of the application** would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure in the application as filed.

The Examiner has not furnished any specific reasons why the skilled artisan would not deem that the inventor had in fact possession of replication-defective adenoviruses encoding a cytokine gene operatively linked to an endogenous or heterologous promoter to treat a tumor in a

patient. Rather, the Examiner has made a general allegation that "an adequate written description of such adenovirus requires more than a mere statement that it is part of the invention."

Applicants submit that this general allegation does not in any manner establish a *prima facie*, case for lack of written description as required in the Guidelines, since no reasons were given whatsoever. This fact alone should render this rejection moot.

Furthermore, under Part II 1, of the Guidelines it is stated that:

> "The absence of definitions or details for well-established terms or procedures should not be the basis of a rejection under 35 U.S.C. § 112, ¶ 1. for lack of adequate written description."

Applicants submit that endogenous promoters and heterologous promoters were well known terms in the art at the time of filing this application and therefore a detailed definition is not necessary.

Moreover, the Guidelines also require that in issuing a rejection for lack of written description, a review of the entire application is required and:

> "Such a review is conducted from the standpoint of one of skill in the art at the time the application was filed and should include a determination of the field of the invention and the level of skill and knowledge in the art. (Guidelines, ll 2.)"

See also, *Wang Laboratories v. Toshiba Corp.*, 993 F2d 858,865, 26 USPQ2d 1767,1774 (Fed Cir. 1993) which supports the above.

The Examiner was silent with respect to why one skilled in the art would deem that the inventors did not have possession of endogenous promoters and heterologous promoters. In fact the Examiner did not even mention the skilled artisan in rendering this rejection. Nor did the

Examiner assess the level of skill and knowledge in the art. Applicants submit that the skilled artisan at the time of filing this application not only knew of endogenous promoters and heterologous promoters, but a laboratory technician, one less than those skilled in the art at the time of filing the present application, could easily substitute without undue experimentation one promoter for another in the adenoviral vector construct described in the present specification.

Moreover, the Examiner has not presented any reasons why a person skilled in the art cannot construct a defective adenoviral vector encoding more than one cytokine in view of the teachings at page 15 and page 16 of the application as filed.

In summary, the Examiner has failed to meet the required burden for this 35 U.S.C.§ 112 first paragraph rejection because:

1. there were no reasons given for this rejection;

2. there was no assessment of the level of those skilled in the art at the time of filing this application; and

3. there was no indication why the skilled artisan would deem that the inventors did not have possession of the invention at the time of filing thereof.

Therefore, Applicants submit that a *prima facie* case of lack of written description has not been established and therefore this rejection cannot be maintained. Withdrawal of this rejection is respectfully requested.

3) Claims 15 to 22 have been rejected under 35 U.S.C. § 112, first paragraph as being nonenabled. As far as this rejection may pertain to the current claims of record, this rejection is respectfully traversed.

First of all, the current claims of record are directed to a method for treating a tumor by injecting the defective adenoviral vector which comprises a cytokine selected from the group of interleukin-2 and gamma-interferon. Thus, the majority of the Examiner's rejection with respect to lack of enablement is rendered moot; i.e., the issue concerning "administering the vector into cells which infiltrate said tumor," part of the issue concerning the "various cytokines;" and the issue concerning the "essential sequences need for encapsidation."

Thus, one of the remaining issue in this rejection pertains to the heterologous promoter and the endogenous promoter. First of all, the Examiner's attention is directed to at least page 14, lines 3 to 26, in which a variety of promoters are disclosed, which can be used in replacement of the MLP promoter such as the LTR of RSV, the IE gene of CMV and the like described therein.

It cannot be denied at the time the application was filed that the skilled artisan knew what an endogenous promoter and a heterologous promoter were. Moreover, it cannot be denied that a person skilled in the art could easily substitute one promoter for another at the time of filing this application. In fact, any laboratory technician- a person less skilled in the art, could exchange one promoter for another without undue experimentation and with a reasonable expectation of success at the time the present application was filed.

Using different promoters to express nucleic acid sequences was established in this art since the early 80's. Indeed, as stated in *Hybritech Inc v. Monocional Antibodies, Inc.,* 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1983), *cert. denied.* 480 U.S. 94 (1987):

> "A patent need not teach, and preferably omits, what is well known in the art."

Furthermore, the Examiner has not provided sufficient reasons why the skilled artisan could not make such a simple well known laboratory manipulation to create a defective adenoviral vector which has a different promoter or why it would require undue experimentation.

It appears that the Examiner requires that some correlation in the specification be made between different promoters to prove that the various promoters can be used. This is evidenced from the statement in the Official Action, wherein the Examiner stated that "the specification does not correlate the early and late adenoviral promoters such that equivalent expression of cytokine could be obtained."

However, Applicants submit that this requirement is unnecessary to establish enablement. The Examiner is referred to *Ex Parte Cole*, 223 USPQ 94 (PTO Bd. App. 1983) where the Board stated the following:

> "Claims are addressed to the person of average skill in the particular art. Compliance with 112 must be adjudged from that perspective, not in a vacuum. It is always possible to theorize some combination of circumstances which would render a claimed composition or a claimed method inoperative, but the art-skilled would assuredly not choose such combination. We know of no statutory or case law requiring each and every compound within a claim to be equally useful for each and every contemplated application"

Moreover, Applicants would like to point out that the showing of an equivalent expression of a cytokine is not necessary to achieve a therapeutic effect. The issue is whether the amount expressed has a therapeutic effect, irrespective of equivalency.

Finally, Applicants are enclosing the following publications which illustrate the use of promoters other than the MLP in a defective adenoviral vector and the achievement of tumor reduction with the different promoters:

(1) Sios at el (Annex I) disclose an adenoviral vector with an IL-2 gene driven by either the CMV or RSV promoter. Using these two promoters a 17% and 42% reduction in tumors was achieved;

(2) Iqbal Ahmed at al (Annex 2) disclose a replication defective adenoviral vector expressing human IFNa2b under the control of the CMV promoter. After injection of this vector complete regression of the tumor resulted.

(3) Stewart et al, of record, disclose a replication defective adenoviral vector expressing human IL-2 under the control of the CMV promoter in phase I clinical trials and tumor regression was demonstrated.

All of these references illustrate that other promoters, other than the MLP promoter can be used in defective adenoviral vector constructs resulting in tumor regression. Stewart at al use an AdCa IL-2 adenoviral vector which is deleted in the El and E3 regions, which is a similar construct to that in the present invention.

Thus, Applicants submit that the present invention is enabled for endogenous and heterologous promoters.

With respect to new Claim 24, Applicants submit that it would not be undue experimentation to obtain the level of GM-CSF known to obtain a therapeutic effect.

Indeed, Fujii et al, a copy of which is enclosed as Annex 3, teach similar amounts of injected cells as those taught in the present invention and a therapeutic effect was in fact achieved. The specification gives specific guidelines at least on page 12 for quantification of the amount of cytokines using ELISA, which is exactly what Fujii et al described.

Moreover, with respect to Claim 25. the introduction of more than one cytokine was a well known technique. If results are in fact achieved as the Examiner has admitted on record with IL-2 or λ-IFN, Applicants submits that other cytokines in combination would easily achieve the therapeutic effect.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

35 U.S.C. § 112, second paragraph

Claims 15 to 22 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite. This rejection has been rendered moot by the claim amendments. Therefore, withdrawal of this rejection is respectfully requested.

35 U.S.C. § 103(a)

1) Claims 15 to 22 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Barber (U.S. Patent 5,662,896) in view of Rosenfeld. For the following reasons, this rejection is respectfully traversed.

It should first be brought to the Examiner's attention that U.S. Patent 5,662,896 filed on March 17, 1993 is a continuation-in-part of Ser. No. 965,084 filed October 22,1992, abandoned, which is a continuation of Ser. No. 586,603 filed September 21,1990, abandoned, which is a continuation-in-part of Ser No. 565,606 filed August 10, 1990, which is a continuation-in-part of Ser. No. 395,932 filed August 18, 1989, abandoned, which is a continuation-in-part of Ser. No. 170,515, filed March 21, 1988 abandoned.

The priority date of the present application is March 16, 1992.

The Examiner maintains that Barber taught administering a retroviral

vector encoding a cytokine in a pharmaceutical carrier intratumorally and cites claim 1 for support. However, Applicants have reviewed U.S. serial No. 965,084 filed October 22, 1992 (after Applicants priority date) as well as U.S. serial No. 565,606 filed August 10, 1990 (prior to Applicant's priority date) and there was no disclosure in these applications of intratumoral injection as in issued U.S. Patent 5,662,896. The remaining applications were not available to the Applicants at the present time and even one application, U.S. application 586,603, is apparently lost and has been placed on Official Search.

Therefore, since a series of continuation-in-parts were filed prior to the issuance of Barber, it appears that the added subject matter can only be given the date of disclosure of the filing date of the Barber patent, which is March 17, 1993, after Applicants' priority date. Therefore, it appears that Barber is not prior art with respect to the disclosure of intratumoral injection.

Prior to discussing Rosenfeld et al, Applicants would like to set the record straight with respect to the Examiner's comments that "the late promoter is a heterologous promoter because the adenoviral late promoter is heterologous to the cytokine." A skilled artisan, reading Applicants' specification would not interpret the meaning of a heterologous promoter in this manner. A promoter is a region of DNA involved in binding of RNA polymerase to initiate transcription. Heterologous means derived from or associated with a species different from that being referred to. Therefore, the heterologous promoter is from a different species than the adenovirus, not from the cytokine as the Examiner maintains.

Rosenfeld et al is mainly concerned with the transfer of the alpha-1 antitrypsin gene to the lung epithelium *in vivo*. For this purpose Rosenfeld et al teaches a replication-defective

adenoviral vector lacking ElA and E3 regions and containing in replacement of the EIA region, the human alpha-1 antitrypsin gene driven by the MLP promoter. Intratracheal administration of this construct resulted in expression of the human alpha-1 antitrypsin gene in the respiratory epithelium of rats.

It is not surprising that successful delivery to respiratory epithelium was accomplished since adenoviruses are normally trophic for respiratory epithelium. However it was not known nor demonstrated in neither Barber nor Rosenfeld at al that the adenoviral vector could penetrate tumors.

Indeed, the presently claimed invention is directed to a method for treating a tumor in a patient using a replication-defective adenoviral vector lacking the ElA, ElB and E3 regions. The Rosenfeld at al reference addresses lung administration and is silent with respect to intratumoral delivery and cytokine expression. There is no teaching or suggestion in Rosenfeld at al that any other genes can be transferred using their adenoviral vector other than those to treat lung hereditary disorders such as cystic fibrosis. This is completely different than what is presently claimed in the present invention.

Moreover, it should be emphasized that to achieve expression of cytokines in tumor cells, it was necessary to demonstrate that any vector, including the adenoviral vector as currently claimed could be capable of penetrating tumor regions and expressing the cytokines within the tumor cells(see, Russell of record).

It was known prior to the filing date that tumor tissue is indeed highly disorganized and heterogenous. The tumor can be highly vacularized or can be less vascularized or poorly vascularized and therefore difficult for a vector to penetrate. Without such a disclosure in the

prior art that poorly vascularized tumor regions can be penetrated by an adenoviral vector, Applicants submit that it would not even be predictable to achieve cytokine expression with an adenoviral vector with any chance of success.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

2) Claims 15 to 22 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Nabel (U.S. Patent 6,297,219) in view of Crystal (U.S. Patent 6,013,638). For the following reasons, this rejection is respectfully traversed.

Nabel, U.S. Patent 6.297,219 discloses a method of treating tumors using systemic administration by intravenous, intramuscular or subcutaneous injection. Indeed, the bulk of this patent is directed to a method of introducing genetically-altered endothelial cells into the vascular wall by arterial catheterization. Therefore, there is no working evidence of record in Nabel's patent that the intratumoral administration of cytokine-expressing adenoviral vectors works *in vivo* to provide tumor growth inhibition. Rather, Nabel discloses the use of specialized catheters for delivery to endothelial tissues or alternatively, the therapeutic gene product can be secreted into the circulation which perfuses specific tissues or organs.

We have reviewed the priority document, U. S. Serial No. 07/331,366 filed March 31, 1989, of the Nabel patent. Cytokines are not even mentioned among the suitable therapeutic genes that can be introduced by these methods (see, page 27 and 28 of the priority document). Indeed, as far as cancer treatment is concerned, Nabel's disclosure envisages the transfer of cells expressing genes encoding diphteria toxin, pertussis toxin or cholera toxin and to introduce the transformed cells in proximity to the malignancy (See. page 28, lines 3 to 5).

Indeed, Nabel envisages the delivery of DNA or RNA sequences to tumor cells in vivo using (1) retroviral or viral vectors, (2) DNA or liposome complexes, (3) chemical formulations containing DNA or RNA sequences coupled to a carrier molecule, or (4) utilizing cell-mediated transfer, as disclosed in the paragraph bridging pages 27 and 28.

Furthermore, in addition to retroviral vectors, Nabel recites a variety of vectors such as those from adenovirus, papillomarvirus, herpes virus, parvovirus and the like. Genes which may be used in this context are any sequence encoding an intracellular, secreted or cell surface molecule which is exogenous to the patient and which is immunogenic to the patient, induces rejection, regression or both, of the tumor or are immunostimulant genes which could be suitably transferred to the cancerous patient, most of them being of human origin and thus endogenous to the patient (See, page 32 line 11 to page 33, line 4).

It should be noted that IL-2 and IFNgamma represent only two choices out of forty (40) possibilities. In fact, Nabel discloses so many different possibilities concerning the vector, the genes to be expressed that it is only through hindsight that one could determine that Nabel teaches the presently claimed invention.

Moreover, Nabel fails to disclose that the adenoviral vector lacks the E1A, ElB and E3 regions of the adenovirus. There is no disclosure that the adenoviral vector can in fact penetrate into a tumor and achieve expression on a therapeutic level, as disclosed in the present invention. In fact, there is no working example that expression of any viral vector, including an adenoviral vector can be achieved in tumor cells.

Once more it should be emphasized that it was known prior to the filing date that tumor tissue is indeed highly disorganized and heterogenous. The tumor can be highly vacularized or

can be less vascularized or poorly vascularized and therefore difficult for a vector to penetrate. Without such a disclosure in the prior art that poorly vascularized tumor regions can be penetrated by an adenoviral vector, Applicants submit that it would not even be predictable to achieve cytokine expression with an adenoviral vector with any reasonable expectation of success from the disclosure of Nabel.

Crystal, U.S. patent 6,013,638 discloses replication defective adenovirus vectors encoding various therapeutic genes and their use for delivering therapeutic gene products to the lungs. The working examples illustrate adenoviral vectors deleted in the El and E3 regions and containing in replacement of the El sequences, either the alpha-1 trypsin gene or the CFTR under the control of the MLP promoter. The adenovirus constructs are then administered through direct instillation into the trachea of anesthetized rats. As a result, the presence of gene transcripts could be detected for a period of time. Crystal also disclose that aerosol administration could be employed to target lungs.

The method described in the presently claimed invention differs from the disclosure of Crystal at al by the type of administration; i.e., intratumoral administration, whereas Crystal teaches local administration by instillation or aerosol to deliver the therapeutic genes into the lungs. Aerosol administration refers to inhalation of the product that has been treated by jet or ultrasonic nebulization, whereas instillation can be defined as administration of a liquid drop by drop. Therefore, both techniques disclosed by Crystal et all differ from intratumoral administration.

Again it should be emphasized that it was known prior to the filing date that tumor tissue is indeed highly disorganized and heterogenous. The tumor can be highly vacularized or can be

less vascularized or poorly vascularized and therefore difficult for a vector to penetrate. Without such a disclosure in the prior art that poorly vascularized tumor regions can be penetrated by an adenoviral vector. Applicant submits that it would not even be predictable to achieve cytokine expression with an adenoviral vector with any expectation of success.

As stated in *In re Vaeck*, 947 F 2d. 488. 20 USPQ2d 1438 (Fed. Cir. 1991) to establish a case of obviousness," both the suggestion and the reasonable expectation of success must be founded in the prior art." Applicants submit that there is no reasonable expectation of success found in any of the cited prior art.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Summary

Based on the foregoing, a favorable action in the form of a Notice of Allowance is respectfully requested and earnestly solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

Please amend the first paragraph after the heading as follows:

This application is a continuation application of U.S. application serial no. 09/204,427, filed December 3, 1998, which is a continuation of 08/619,157, filed March 21, 1996, abandoned, which is a continuation of [08/469,777] 08/469,773, filed June 6, 1995, abandoned, which is a continuation of 08/150,011, filed January 13, 1994, abandoned, which was the national phase of PCT/FR93/00264, filed March 16, 1993 as WO/9319191.

In the Claims

15. (Once Amended) A method for treating a tumor in a patient in need of such treatment, said method comprising injecting an effective amount of a pharmaceutical composition into said tumor wherein said pharmaceutical composition comprises:

b. an adenoviral vector [comprising a genomic sequence of an adenovirus wherein said genomic sequence] wherein said adenoviral vector:

i. is replication-defective and lacks the EIA. EIB and E3 regions of said adenovirus [in that said adenovirus lacks a sequence needed for its replication, but which contains those sequences which carry genetic information needed for the corresponding adenovirus to enter cells which said adenovirus is capable of infecting;

ii. comprises a set of essential sequences needed for encapsidation of said adenovirus]; and

[iii] (ii) comprises [an insert containing] a nucleic acid sequence coding for a cytokine, [wherein said insert is] under the control of an endogenous or heterologous promoter; and wherein said cytokine is interleukin-2 or gamma-interferon [adenovirus vector lacks the transactivators ElA and ElB and the E3 region of the adenovirus]; and

c. a pharmaceutically acceptable vehicle.

16. (Once Amended) The method according to Claim 15, wherein [the genomic sequence of the adenovirus lacks its 5' end region downstream of] said adenoviral vector retains the early promoter of the ElA region of the adenovirus, and wherein the nucleic acid sequence coding for the cytokine is [placed] under the control of [this] said early ElA promoter.

17. (Once Amended)The method according to Claim 15, wherein said nucleic acid sequence coding for said cytokine is [placed] under the control of an adenovirus late promoter.

18. (Once Amended)The method according to Claim 15, [wherein the genomic sequence of the adenovirus has a heterologous promoter and] wherein said nucleic acid sequence coding for said cytokine is [placed] under the control of said heterologous promoter.